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Contents lists available at ScienceDirect

Journal of Ayurveda and Integrative Medicine

journal homepage: <http://elsevier.com/locate/jaim>

Review Article

Pathophysiology of Covid-19 and host centric approaches in *Ayurveda*

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ARTICLE INFO

Article history:

Received 19 June 2020

Received in revised form

23 November 2020

Accepted 25 November 2020

Available online xxx

Keywords:

Complimentary medicine

Physiopathology

Ayurveda

SARS COV-2

Host centric

Prophylaxis

ABSTRACT

The world is facing a global crisis and health emergency of COVID-19. Understanding of COVID-19 pathophysiology in ayurvedic host centric framework is prerequisite for apt use of *Ayurveda*. This paper reviews COVID-19 pathophysiology, clinical presentations and prognosis in ayurvedic perspective. Concept of exogenous pathogenic diseases can be traced in fever, microbes, toxins, epidemics and seasonal regimens chapters of *Ayurveda*. Such exogenous diseases later manifest multi-system presentation according to involvement of different 'Doshas' and derangement of 'Agni'. The pathology of COVID-19 is primarily that of *Sannipata Jwara* (fever) with involvement of respiratory system. Secondary manifestations include coagulopathies, cardiovascular, neural, and renal complications. Gastrointestinal system is closely associated with respiratory mechanism in *ayurvedic* pathophysiological conceptualization of *Srotas*. Abnormal immune responses in COVID-19 are result of abnormalities of *Tridosha*, *Rakta* (blood) and *Ojus* (Vital nectar). The initial phase is *Vata-Kapha* dominant whereas later stage of aggravated immune response is *Vata-Pitta* dominant. Alveolar damage, coagulopathies indicate *Rakta dhatu* vitiation. With this integrative understanding of COVID-19, we propose novel strategies for therapeutics and prophylaxis. Measures for 'Conservation of Agni-bala', 'Attainment of Rakta-Pitta-Prana homeostasis and 'Protection of Tri-Marma i.e. vital organs' can be important Host based strategies for reduction in the mortality in COVID-19 and for better clinical outcomes. This host centric approach can make paradigm shift in management of this epidemic.

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1. Introduction

The world is facing a never like pandemic of COVID-19 with its implications at economical, psychological and more levels in society. Pragmatic strategies are being proposed for possible role of *Ayurveda* in management of COVID-19 [1]. Scientists are proposing need of 'Systems approach' as it can provide more comprehensive structure to manage disease as well as epidemic components, as society is itself a complex adaptive system [2]. Potential of Ayurvedic immunomodulators (*Rasayana*) medicines and need of host centric approaches are proposed by the time [3,4]. The need for 'host centric approach' gets underlined amidst recurrence (of infection and disease) in cured patients of COVID-19 [5].

Understanding COVID-19 Pathophysiology is basic prerequisite for deciding *Ayurveda* preventive and curative strategies. One cannot appropriately bridge *Ayurveda* with evidence based

medicine without understanding epistemology of *Ayurveda* [6]. *Ayurveda* deals at more comprehensive levels of abstraction like *Dosha* and *Dhatu* (tissues). Thus an appropriate translation of COVID-19 in *Ayurvedic* anatomical and pathophysiological terminology is needed. This article reviews COVID-19 pathology and its *Ayurvedic* perspective and discuss host centric approach of *Ayurveda* for COVID-19.

2. Infectious diseases in *Ayurveda*

The concept of pathogenic agents and infectious disease was not unknown to *Ayurveda*. Fundamentally *Ayurveda* classifies diseases as *Nija* (from Intrinsic Causes), *Agantuja* (Extrinsic causes) and *Manasa* (Psychosomatic). *Aupsargika* (Infectious) and *Sankramak* (Contagious) are mentioned by Sushruta (7th century BC). The concept of infectious diseases is explained under five chapters *Jwara*, *Krimi*, *Visha*, *Janapadodhwamsa* and *Ritucharya* (Seasonal regimes). *Jwara* (Hyperthermia) is cardinal symptom in many of infectious diseases. *Krimi* is all encompassing term used for parasites, worms and microbes. Arundatta the commentator of *Ashtang*

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Peer review under responsibility of Transdisciplinary University, Bangalore.

Hridaya clarifies that pathogen of the blood is totally invisible to the human eye, their existence can be inferred [7].

Janapadodhwamsa is the concept of epidemics in *Ayurveda*. *Ritucharya* is the season specific regimes where prophylaxis and management of seasonal flu can be seen. Autumn and spring fevers are associated with *Pitta* and *Kapha* dominance [8]. Role of seasonal changes in environment, particularly temperature and humidity are proven to be associated with modifications in host intrinsic, innate, and adaptive immune responses to viral infections in the respiratory tract [9] (Fig. 1).

'*Dosha*' and '*Agni*' are the pivotal concepts as imbalance or balance of *Dosha* and *Agni* are synonymous with state of disease or being healthy. Even in exogenous diseases, there is the role of *Dosha* and *Agni* in disease manifestation and prognosis. *Dosha*, *Dhatu*, *Mala*, *Srotas*, *Agni* and *Manas* (mind) is the framework in which any disease is needed to be interpreted. Concept of diagnosis in *Ayurveda* is less about naming diseases but understanding the underlying in-equilibrium. Charaka says that innumerable diseases can origin from same vitiated *Dosha* according to variations in aetiology and involved body tissues [8]. With these insights COVID-19 is reviewed here.

3. Understanding COVID-19 disease & Ayurveda

3.1. The virus and Ayurveda

Coronaviruses is a genus in the Coronaviridae family (order Nidovirales) of pleomorphic and enveloped viruses. Three human coronaviruses HCoV-OC43, HCoV-229 E and SARS CoV-1 were acknowledged as pathogenic agents for upper respiratory tract infections [10].

Although not mentioned as virus but microbes and pathogenic agents are described in *Ayurveda* as reviewed earlier. The initial stage of COVID-19 is exogenous (*Agantu*) disease which later converts into systemic (*Nija*) disease [11]. *Abhishangaja Jwara* is the term for those caused by the contact of the poisonous air or toxic plants or other such toxins [11]. However this *Abhishangaja*

Jwara later complicates with involvement of multiple tissues and organs.

3.2. The epidemics/contagious complement and ayurveda

According to few reports SARS-CoV-2 can be detected in the air, three hours after aerosolisation. WHO has issued guidelines for contact and droplet precautions for healthcare workers working for suspected COVID-19 patients, also USA-CDC has recommended airborne precautions [12].

Janapadodhwamsa is the Ayurvedic term for epidemics. *Janapada* refers to particular geographic consideration. Interestingly there is mention of an epidemic fever with respiratory system presentation (fever, cough, breathing difficulty, rhinorrhoea, headache and even anosmia) caused by entry of pathogenic agent through the nasal passages. This clinical presentation by Sushruta is amazingly analogous to epidemics like SARS, MERS, Swine Flu and even COVID-19 [13]. Contagious diseases and means of contagion as physical contact, inhalation, eating together, sleeping, sitting together and sharing used linens and garlands are well discussed by Sushruta.

3.3. Stage wise disease progression, immune response, lung events and ayurveda

There are four stages of Disease progression viz Asymptomatic Stage, Stages with upper and Lower Respiratory tract involvements and last Stage of ARDS/MODS. The disease progression and stage-wise Immune Responses are summarised in Table 1.

Events in Lung and Ayurveda Perspectives (Table 2).

3.4. Symptomatology, cytokine storm and Ayurveda

Symptoms include aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell. A rash on skin and discoloration of fingers or toes are less common symptoms. Serious symptoms include difficulty breathing or shortness of breath, chest pain or pressure, loss of speech or movement. Nasopharyngeal swab Polymerase chain reaction analysis confirms the disease.

3.4.1. Respiratory symptoms in Sannipata Jwara

Abhishangaja Jwara, *Bhootopasangaja Jwara* is *Vishama Jwara* according to *Vagbhata*. *Sannipatika* is a disease variant with vitiation of all three *Dosha* in pathogenesis. *Agantuja* varieties of any diseases can complicate into *Sannipatika* state with severe prognosis. The viral or bacterial fevers, along with malignancy, auto immune diseases, etc. are needed to be considered as *Sannipatika* state. In COVID-19 Primary manifestations are seen at *Pranavaha Srotas* as virus enters through nasal passage (Table 3).

Respiratory symptoms are seen in different types of *Sannipata jwara*.

The most mimicking '*Kanthkubja Sannipata*' symptoms include throat pain, dyspnoea, tastelessness, delirium, Malaise, dehydration, head ache, shaking [25]. Out of the 29 *Lakshanas* of *SarvaDoshaSannipata*, 25 *Lakshanas* are found in the COVID-19 infection [26].

To summarize, the early presentation of COVID-19 is '*Kapha Vata*' dominant whereas late phase of complications is '*Vata Pitta*' dominant. The later phase of secondary infections, sepsis & multi organ failure is indicative of involvement of '*Marma-Asthi-Sandhi Roga Marga*' (disease pathway).

Abhishangaja Jwara, *Bhootopasangaja Jwara* is *Vishama Jwara* according to *Vagbhata*, *Sannipatika* is a disease variant with vitiation of all three *Dosha* in pathogenesis [27]. *Agantuja* varieties of

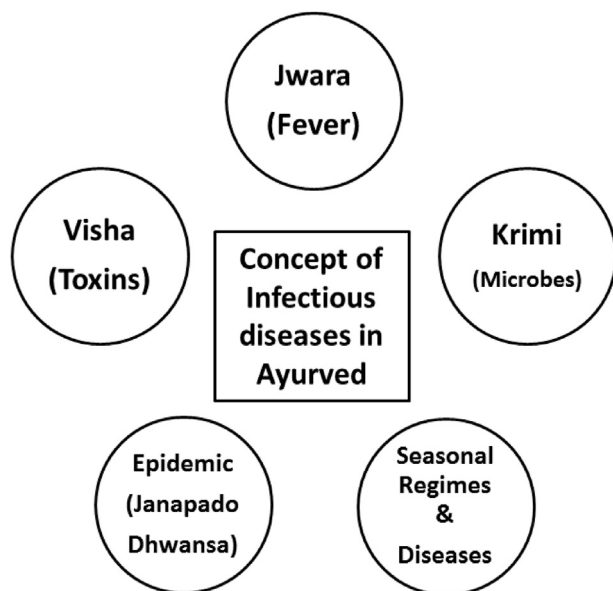


Fig. 1. Concept of Infectious diseases in Ayurveda

Table 1
COVID-19 Disease Progression: Pathophysiology and Immune Response.

Disease progression	Local pathophysiology	Stage wise immune response
Stage 1 Asymptomatic stage	Entry of virus in nasal passage Epithelial cells (particularly Ciliated cells) get affected [14]. ACE2 is important receptor along with TMPRSS2 [15,16].	Mild Innate immune response. Th1 response by host is crucial to decide fate of infection.
Stage 2 Upper Respiratory Tract involvement	Although less viral load, individuals are infectious. Sputum swab exhibit SARS CoV-2 In few Cough, sore throat starts here. In most cases progression ends here.	Strong Innate immune response. Increased plasma IP-10, MIG, IL- 8 and MCP levels during the first week are considered independent predictor of outcome & with adverse outcome. (intensive care unit admission or death) [17,18]
Stage 3 Lower Respiratory Tract involvement	Virus starts affecting alveoli. It affects type II pneumocytes (responsible for production of surfactant and are precursor for type I pneumocytes) than type I pneumocytes (responsible for gaseous exchange). Type II pneumocytes undergo apoptosis and die due to viral particles [19]. DAD: Diffuse alveolar lung damage: This is most commonly seen histopathologic feature [21]. Histologically: Injury to the alveolar epithelial cells, Hyaline membrane formation, Hyperplasia of type II pneumocytes, Consolidation by fibroblastic proliferation with extracellular matrix and fibrin forming clusters [22]. Alveolar macrophages affected: Alveolar macrophages expressing ACE2 are again target cells for SARS-CoV-2 infection. Alveolar condensation, Ground glass infiltrations, Hypoxia	Aggravated immune response: Cytokine storm: lower lymphocyte counts and higher plasma concentrations of a number of inflammatory cytokines such as IL- 6 and tumor necrosis factor (TNF) [20]. Crucial role of T cells: Another study reported that CD4+ T cells, CD8+ T cells, and natural killer cells were reduced in severely ill patients compared with those with mild disease symptoms. Moreover, a substantial reduction of CD4+ T cell and CD8+ T cell counts in the peripheral blood was also observed in a patient who died [23].
Stage 4 ARDS, MODS	Acute Respiratory Distress Syndrome Pulmonary thrombosis HLH-like (haemophagocytic lymphohistiocytosis) cytokine storm with characteristics of HLH, including hypercytokinemia, unremitting fever, cytopenias, hyperferritinemia, and multi- organ damage, are commonly seen in seriously ill patients with COVID-19 [20].	Raised Serum Ferritin (doubling in 24 h) and raised IL-6, LDH, D- dimer, C-reactive Protein (CRP) levels mark severe condition.

any diseases can complicate into *Sannipatika* state with severe prognosis. The viral or bacterial fevers, along with malignancy, autoimmune diseases, etc. are needed to be considered as *Sannipatika* state [28]. Primary manifestations are seen at *Pranavaha Srotas* as virus enters through nasal passage.

3.4.2. Understanding Cytokine storm in Ayurveda Perspectives

Cytokine storm is overreaction of immune system exhibiting numerous cytokines and resulting in inflammation/necrosis of internal organs, and organ failure. It can be tempting for *Ayurveda* authors to compare cytokine storm with aggravated *Vata*,

Table 2

Lung Events and *Ayurveda*. Importantly COVID-19 lung pathology is more restrictive than obstructive as it is more an alveolar diseases than airway disease, the basic lung pathology classification. Pathological events in lungs and *Ayurveda* Perspectives are summarized in this table

Lung pathology	<i>Ayurveda</i> pathophysiological interpretations
Diffuse Alveolar Lung Damage: Type II pneumocytes hyperplasia Diffuse alveolar damage with presence of multinucleated pneumocytes. Fibro-granulation tissue proliferation in small airways and airspaces (organizing pneumonia-like lesions) in subpleural locations in some patients [23]. Some studies report along with classical DAD, there are evidences of: Capillary injury Mural and luminal fibrin deposition Infusion of the inter-alveolar septa by Neutrophils/macrophages.	Embryologically lungs are made of bubbling in <i>Rakta</i> (blood) <i>Dhatu</i> . The airsacs represent bubbles, whereas the alveolar composite structure is made from <i>Rakta</i> . COVID-19 is Alveolar disease and thus ' <i>Rakta Dhatu</i> ' remains pivotal in pathology. Type II pneumocytes which serve as precursor for Type I pneumocytes and those produce surfactants get affected. This Regenerative ability of cells/tissue is attributed to <i>Rasa & Shukra Dhatu</i> the first and last tissue in hierarchy of body tissues. <i>Ayurvedic Rasayana & Vajikarana</i> medicines have regenerative efficacies. The word exudate is derived from latin "exsudare", literally meaning 'to sweat out'. Exudative inflammation is like <i>Vishyandana</i> , <i>Ayurvedic</i> term indicating phenomenon of liquefaction. This further result in alveolar condensation. The hyaline membrane formation and obstruction is nothing but <i>Avarodha</i> (Obstruction) by <i>Kapha</i> in turn leading to further vitiation of <i>Vata</i> .
Hyaline membrane formation: A membrane composed of proteins and dead cells lines the alveoli, making gas exchange difficult or impossible, Alveolar condensation	Only <i>Kapha</i> is not necessarily responsible for obstructive phenomena. Even <i>Vata</i> subtypes may obstruct each other. COVID-19 symptoms like anosmia, ageusia and impaired <i>Bala</i> (immunity) are seen as symptoms of ' <i>Prana Avruta Vyana</i> ' [24]. ' <i>Prana Avruta Vyana</i> ' is condition when <i>Prana Vata</i> (<i>Vata</i> subtype responsible for pulmonary and nervous and cognitive functions) obstructs <i>Vyana Vata</i> (<i>Vata</i> subtype for cardio-pulmonary pumping and <i>Bala</i> i.e. strength and immunity) This can be <i>Upadrava</i> (complication) or <i>Udarka</i> (residual effect) <i>Khara Paka</i> i.e. abnormal metabolism leads to hardening of tissues/fibrotic changes. It will be interesting to see if these post COVID-19 fibrotic changes are therapeutically reversible or not. They can be called as <i>upadrava</i> (Complications) or <i>Udarka</i> (residual effect of the disease that is not relieved by the specific treatment) of COVID-19
Interstitial widening and patches of Lung fibrosis	

Table 3
Respiratory symptoms in Sannipata Jwara.

Symptoms	Variant of Sannipata Jwara	Classic
Pratishyay (Rhinorrhoea)	Diminished Kapha, moderate Pitta & increased Vata Sannipata	Charaka Samhita
Kasa (Cough)	Increased Kapha –diminished Vata and Pitta Sannipatika, Increased Vata and Kapha & diminished Pitta Sannipata	Charaka Samhita
Shwasa (Dyspnea)	Diminished Kapha, moderate Pitta & increased Vata Sannipata Vata Kapha dominant Sannipata	Charaka Samhita BhavaPrakasha
Pleural pain	Diminished Kapha, moderate Pitta & increased Vata Sannipata Vata Kapha dominant Sannipata	Charaka Samhita BhavaPrakasha

aggravated Agni, Dhatu paka (Body tissue disintegration as result of aggravated Agni), Shotha (Inflammation) or diseases like Jwara and Visarpa where the involvement of body tissues can become fatal very rapidly. There cannot be one single comparable phenomenon in Ayurved for cytokine storm. The 'effect' of cytokine storm is seen on vital organs, quoted as Marma in Ayurveda. Heart, brain and kidney are three important Marmas i.e. vital organs which are accounted into Madhyama Rogamarga (middle pathway for manifestation of disease), amongst three Roga marga (three broad based groups of disease pathways).

In Ayurvedic epistemology vyavayee guna (the important attribute of Visha) makes pathogenesis rapid. Gara Visha is the relevant Ayurveda concept of toxins where Gara literally means the one digluted. Ashtang Sangraha has mentioned that Gara Visha (A group of poisons where one can find 'Combination of parts of the body and excreta of different animals enlisted) can be fast acting. Thus Visha is an important consideration as there is speedy and lethal pathogenesis that affects vital organs. The speediness is important virtue of pathogenesis in COVID-19.

3.5. Complications & multi-organ involvement in COVID-19 and Ayurveda

ACE2 receptors are there in many tissues and thus COVID-19 presents as Multi-systemic disease [29].

3.5.1. Gastrointestinal complications

Abundant amount of ACE2 is present in the small intestine and colon, which can be the probable reasoning for gastrointestinal symptoms like diarrhea, nausea, vomiting, and abdominal discomfort or pain. Mild to moderate liver injury (elevated aminotransferases, hypoproteinemia, and prothrombin time prolongation) has been reported. Analysts have suggested that abdominal pain can be used as a clinical predictor of more severe disease and be involved in future risk stratification algorithms [30].

3.5.2. Neural complications

Agitation, confusion, diffuse corticospinal tract signs with enhanced tendon reflexes, ankle clonus, bilateral extensor plantar reflexes, disorientation, and poorly organized movements in response to command, were reported during and or at the time of discharge [31].

3.5.3. Cardiac complications

After respiratory system, the second most affected body system known by COVID-19 is the cardiovascular system [32]. Patients with cardiovascular risk factors are at increased risk to develop severe complications. Some cardiovascular diseases associated with COVID-19 include myocarditis, heart failure, cardiac arrhythmias, and acute coronary syndrome as direct consequences of systemic inflammation [33].

3.5.4. Vascular complications

Reports about association of coagulopathies with poor prognosis and probable role of anti-coagulants like low molecular heparin are published [34]. Elevated D-dimer and FDP (Fibrin Degradation products) are common in deaths with COVID-19. Poor prognosis is also associated with disseminated intravascular coagulopathy (DIC) [35].

In Ayurveda terminology coagulopathies are 'Kapha dominant Raktapitta'. Charaka has mentioned Raktapitta as complication of Jwara. Raktapitta represents a group of pathologies including coagulopathies, vascular complications etc.

3.5.5. Renal complications

The ACE2, is abundant in renal tubular epithelial cells. This can be linkage for some associations between COVID-19 and acute kidney injury (AKI), proteinuria, microhematuria and raised serum creatinine. Acute kidney injury is more common among patients with more severe disease, and is considered a negative prognostic factor with respect to survival [36]. Perhaps a maladaptive systemic inflammatory immune response, cytokine storm may contribute to hypoperfusion and thus result in injury to the renal tubules. Systemic hypoxia, abnormal coagulation are causes and diffuse proximal tubule injury with frank necrosis was evident. There were prominent erythrocyte aggregates obstructing the lumen of capillaries without platelet or fibrinoid material [37].

3.5.6. Sepsis/MODS (Multi Organ Dysfunction Syndrome)

Critically ill COVID-19 patients are reported to develop typical clinical manifestations of shock, with severe metabolic acidosis, indicating possible microcirculation dysfunction and impaired liver and kidney functions [38]. Sepsis in COVID-19 cases have wide range of signs and symptoms of multi-organ involvement, including respiratory manifestations, hypoxemia, renal impairment with reduced urine output, tachycardia, altered mental status, and functional alterations of organs expressed as laboratory data of hyperbilirubinemia, acidosis, high lactate, coagulopathy, and thrombocytopenia [39].

Ayurveda scholars have mentioned similitudes between Sama Sannipatika Jwara with 'sepsis/septic shock/systemic inflammatory response syndrome (SIRS)/multiple organ dysfunction syndrome (MODS)/septic encephalopathy/delirium' [40].

Cardiac, Renal and Neural presentations indicate involvement of Tri Marma (three most vital organs). Hepatic derangements and coagulopathies underline vitiation of Rakta. Involvement of all three Roga marga (Ayurveda diseases pathways) is seen (Fig. 2).

4. COVID-19 in Ayurvedic model of Hetu (Etiology)- Linga (Symptomatology) - Samprapti (Pathogenesis)

4.1. Etiology factor (Hetu) and probability of disease progression

The COVID-19 pathogen is Agantuj (exogenous) 80% patients of COVID-19 remain asymptomatic. Contact with viral material can be

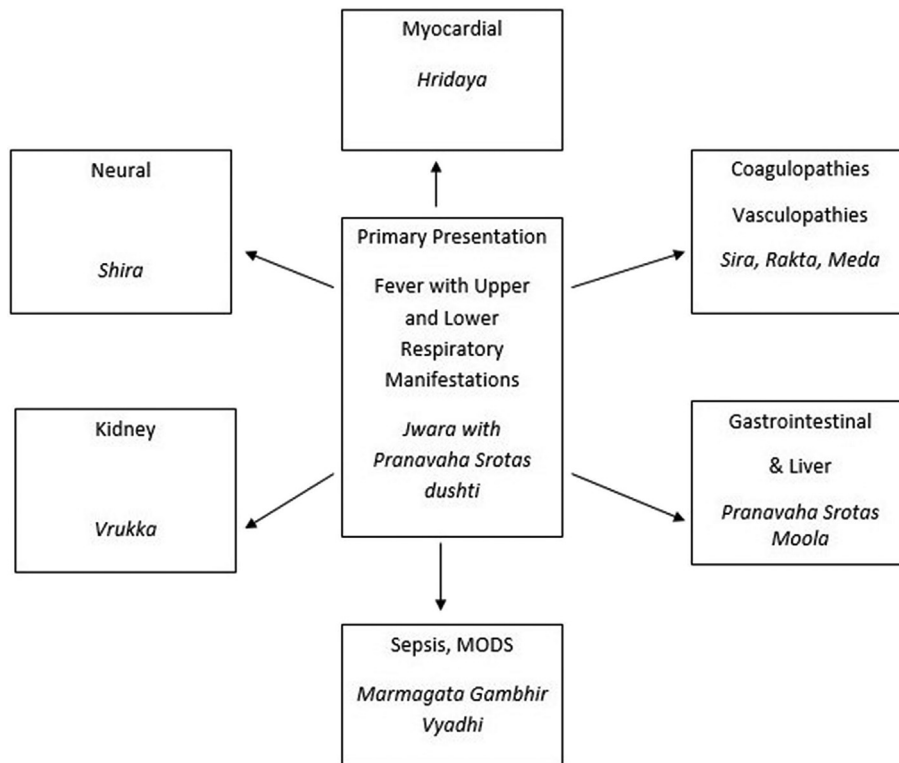


Fig. 2. Primary and secondary manifestations of COVID-19 in Ayurveda perspective.

considered as *Pradhanik Hetu* (etiological factor weak enough to cause disease at its own). SARS CoV-2 can be better interpreted as *Vyanjaka Hetu* (etiological factor acting at time of genesis of disease), whereas *Utpadak Hetu* are etiological factors are mainly diet and lifestyle leading to accumulation of *Dosha*. In Ayurvedic conceptualization accumulated *Dosha* makes the body susceptible to disease. Even in an exogenous disease, there is involvement of *Dosha* and the role of *Agni* in prognosis of disease. As COVID-19 prognosis is associated with comorbidities, this concept of *Utpadaka Hetu* becomes important. Original retrospective studies of non survivors or critically ill cases of COVID-19 can contribute as

evidence for these life style factors as *Utpadaka Hetu* for bad prognosis of COVID-19.

4.2. Linga

The symptoms of COVID resemble with *sannipatika jwara* as reviewed earlier. COVID-19 symptoms are summarized here in Table 4.

Thus there are variety of symptoms showing involvement of *Pranavaha*, *Rasavaha*, *Raktavaha* and *Majjavaha Srotas* and *Marma* involvement. Symptoms are from

Table 4
Analysis of Symptoms in Ayurvedic terminology.

	Ayurvedic name	Common symptoms	Dosha status	Srotas
Fever	Jwara		Pitta dominant Tridosha	
Dry cough	Vata dominant Kasa		Viloma Vata	Pranavaha Srotas
Tiredness	Related with Jwara		Vata dominant	Rasavaha Srotas
		Less common symptoms		
Aches/Pains	Angamarda		Vata dominant	
Sore throat	Galadhwansa		Kapha, (and Rakta vitiation)	Pranavaha Srotas
Rhinorrhea	Pratishyay		Vata, Kapha	Pranavaha Srotas
Conjunctivitis	Netrabhishyanda		Kapha dominant triDosha	Majja vaha Srotas
Headache	Shirashoola		Kapha dominant (and Rakta vitiation)	Raktavaha Srotas
Diarrhoea	Atisara		Vata dominant Tridosha	Purishavaha Srotas
Loss of taste	Aroochi		Kapha, Pitta, Vata	Annavaha Srotas
Loss of smell	Anosmia		Vata	Pranavaha Srotas
Discoloration of fingers	Araktatata, Karshnya		Pitta (and Rakta vitiation)	Raktavaha Srotas
		Serious symptoms		
Difficulty breathing or shortness of breath	Shwasa	Vata- Kapha and Pitta as Shwasa is originated from Amashaya		Pranavaha Srotas, Marma
Chest pain or pressure	Ura Shoola		Vata dominant	Pranavaha Srotas, Marma
Loss of speech or movement	Vakgraha, Vata vyadhi		Vata dominant	Marma involvement

Jwara, Shwasa, Pratishyay, Vatavyadhi, HrudRoga, TriMarma chapters again implying COVID-19 as multi-systemic disease.

4.3. Samprapti

Initial pathogenesis is of *Agantu* (exogenous) *Jwara* and thus exhibit symptoms of *Rasavaha Srotas* i.e. tastelessness, headache, nausea, bodyache. This is followed by symptoms of *Pranavaha* and *Raktavaha Srotas*. *Udana Dushti* is evident as there is extreme loss of *Bala* i.e. deterioration of immune response, speech related symptoms in few. *Raktavaha Srotodusthti* is also evident from coagulopathies and extremity discolorations. Fatal complications are possible because '*Prana*' (vitality or oxygen in this context) follows '*Rakta*' (blood). In *Ayurveda* embryological view point *Fuffusa* (lungs) are made up of *Rakta* only. In context with respiratory

mechanism *Ayurveda* considers the cardiopulmonary unit as a whole without differentiating heart and lungs. *Mahasrotas* (gastrointestinal tract) is also associated with *Pranavaha Srotas* as *moolasthan*. The pathogenesis later involves heart and kidney which are considered as third '*Roga marga*' (disease pathway). In *Ayurveda*, hematuria is seen as associated symptom under *Kasa Roga* (Many Bronchial conditions) indicating involvement of urinary system as complication of respiratory pathologies. Pathogenesis worsens and complicates in ARDS (if there is *kha-vaigunya* i.e. susceptibility in lungs), or involves Heart or Kidney (according to *kha-vaigunya*). Interestingly Hiccup, dyspnea, cough and complications in vital organs are symptoms when fever pathogenesis invades *Majja Dhatu* according to Charaka and Sushruta [8,41]. Thus the later stage of COVID-19 with aggravated immune response indicates invasion of fever in *Dhatu* hierarchy (Fig. 3).

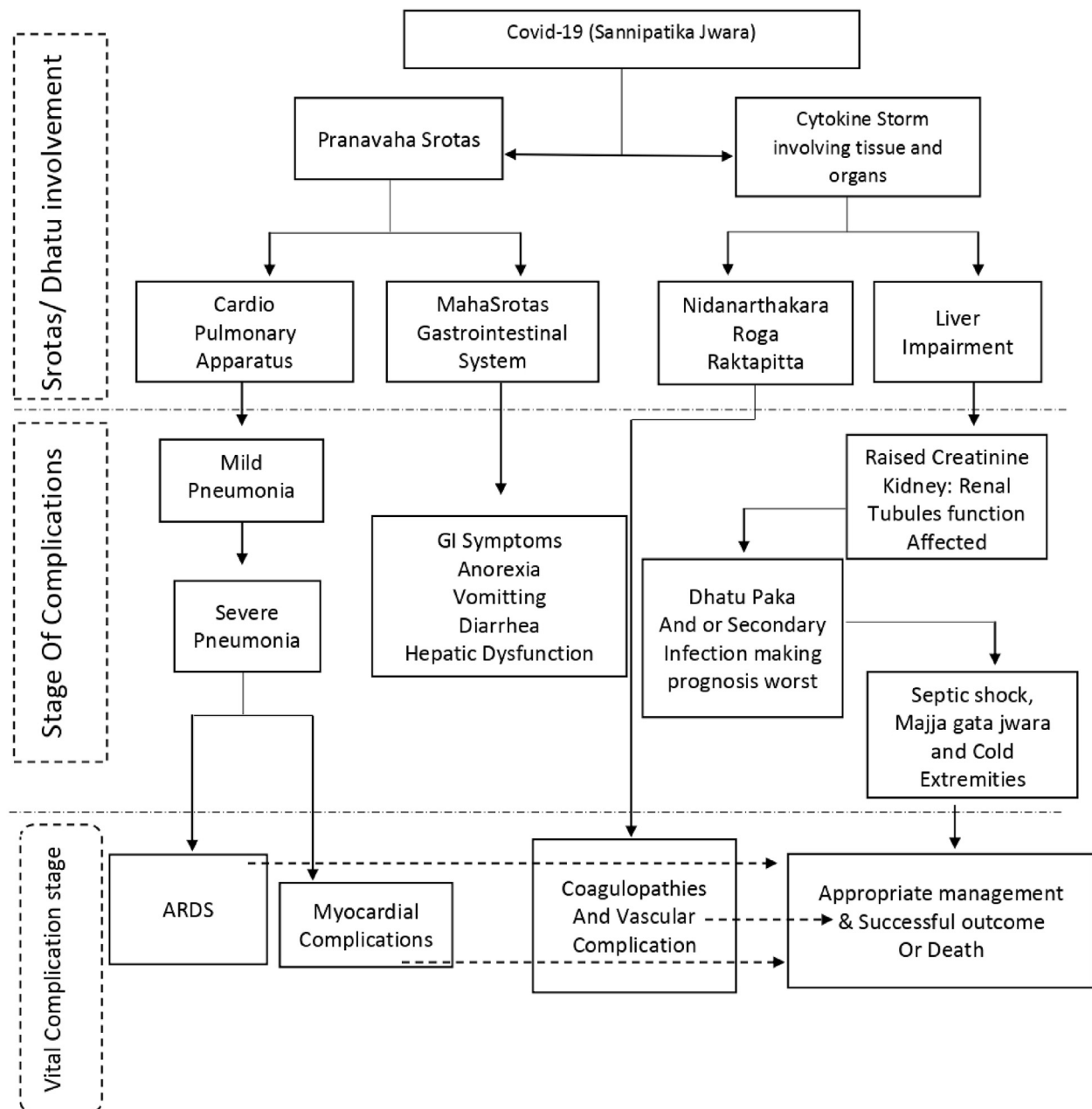


Fig. 3. Stage wise disease progression in Covid-19 integrated approach.

Table 5Contemporary and Novel approaches (Preventive and Therapeutic) based on. *Ayurvedic* Pathophysiology of COVID-19.

Pathogen centric approaches	Host centric approaches	Rationale
Hygiene, Sanitization, Physical Distancing and other measures to avoid possibility of infection.	Contemporary approaches 7–8 H of sleep. Vitamin C, D3 and other supplements. Yoga and Respiratory Exercises. Interventions of Pulmonary Function improving agents	Evidences of immunomodulatory mechanisms of exercise, micronutrients and sleep
<i>Ayurveda</i> Immunomodulator Herbs for minimizing virus replication and to arrest Cytokine syndrome.		Evidences of <i>Ayurveda</i> immunomodulatory herbs/ formulations mechanisms in biomedical terminology
Proposed Novel Approaches based on Host centric Approach and <i>Ayurveda</i> Pathophysiology of COVID-19		
Nasya, Gandusha can be local measures for care of pathogen entry points.	Conservation of <i>Agni-Bala</i> & maintenance of <i>Agni</i> (Digestive and metabolic equilibrium). Attainment of ' <i>Rakta–Pitta-Prana</i> ' homeostasis with specific dietary, lifestyle modifications and therapeutic interventions. Protection of <i>Marma</i> (Vital organs, the dedicated sites of <i>Prana</i>) with specific dietary, lifestyle modifications and interventions ' <i>Prana Kamiya Rasayana</i> ' (<i>Rasayana</i> medicines particularly for vitals). <i>Basti</i> (Medicated enema) and Other relevant measures for protection of Heart, Brain and kidney from relevant chapters like <i>Visha Chikitsa</i> [8].	As <i>MahaSrotas</i> is associated with <i>Pranavaha Srotas</i> as <i>moolasthanas</i> According to <i>Ayurveda</i> Physiology <i>Prana</i> (not mere oxygen but vitality) follows <i>Rakta</i> and both are interdependent [8]. The Inflammatory Responses, Sepsis as well as Coagulopathy are result of <i>Rakta</i> and <i>Pitta</i> vitiation Cytokine storm results in Inflammation and even necrotic changes in vital organs [45]. <i>Basti</i> is recommended as best measure for protection of vital organs [8].
<i>Ayurveda</i> Immunomodulator Herbs for arresting viral load in different organs. This can be decided (from variety of <i>Rasayana</i> Herbs having efficacy on different systems and Organs) on basis of involvement of Organs and Tissues in the patient.		

5. Ayurvedic host centric approach in COVID-19 and remarks

The 'Germ theory' received more importance and was followed by development of Medical Microbiology and anti-microbial medicines in last century. With these advances infectious diseases were treated far well. So far as Host-Germ approach is concerned 'virulence factor theory' was later followed by concept of 'Damage response framework'. DRF is an approach for incorporation of range of host responses to microbes with a parabolic curve in which host damage is plotted as a function of the host response. Importantly neither host nor microbial properties, are adequate to predict the outcome of host–microbe interaction because this outcome exhibits emergent properties [42].

In ayurvedic epistemology, microbe is viewed as *nimitta karana* (instrumental cause), contact of microbe with receptors as *asamavayee karana* (non-intimate cause) and host internal milieu as *samavayee karana* (intimate cause). As reviewed earlier the dynamic status of *Dosha*, *Dhatu*, *mala* and *Agni* the physiological elements of internal milieu are important in fate of exogenous and pathogenic diseases like COVID-19. The disease presentation is a dynamic phenomenon. *Bala* (body strength), *Agni* (digestive power) and *Pradnya* (mental ability) are as markers for prognosis, and *Charaka* has recommended continuous assessment of these three [43]. Thus it is host internal milieu in totality that is important for the immune response and prognosis.

Bala is often considered as body strength but is inclusive of various activities such as immunomodulator, bulk promoting, nutritional etc. [44] Pathophysiology and Immune responses in COVID-19 are important to be discussed in *Ayurveda* perspectives. Immunity is popularly imitated as '*Vyadhikshmatwa*' in *Ayurveda* which is an incomplete translation. *Prana*/vitality is an important consideration. *Rakta* (Blood), *Shukra* (Reproductive tissues and Reproductive hormones) and *Ojus* (Quintessence of the seven body tissues) are the body tissues responsible for immune functions and appropriate immune responses. In fact it is not only immunity but a holistic network of *Bala*, *Agni*, *Dosha*, *Dhatu*, *Bala*, *Vaya* and many more factors that decide the immune responses and fate of disease progression.

Pathophysiology of COVID-19 is primarily that of Respiratory system. Gastrointestinal, cardiac, renal, neural and coagulative complications follow. *Pranavaha Srotas* (Cardiopulmonary apparatus), *MahaSrotas* (Gastrointestinal tract) with *Agni* and *Raktavaha Srotas* (Blood and liver) are vitiated. Earlier presentation of COVID-19 is *Vata-Kapha* dominant whereas later stage of cytokine storm is *Vata-Pitta* dominant. *Rakta* (Blood) is most important *Dhatu* because lung alveolar tissues are made from *Rakta* only, coagulopathies are related with *Rakta* and immune responses too are also associated with *Rakta Dhatu*. COVID-19 affects Pneumocytes type II which are precursor for Type I pneumocytes. Thus reproductive/tissue repairing mechanism of body is another important factor. This reproductive ability is associated with *Shukra Dhatu*. *Ojus* is next important body tissue as vital organs are affected in COVID-19. Thus *Prana-Rakta-Shukra-Ojus* is the pathophysiological quadrant in *Ayurvedic* perspective of COVID-19.

This proposed integrative understanding of Pathophysiology and holistic quadrant of *Prana-Rakta-Shukra-Ojus* can give novel leads for Preventive and Therapeutic approaches for COVID-19. Here we propose Novel approaches (Preventive and Therapeutic) based on this integrative understanding. They are summarized in Table 5.

Last few decades there is a good amount of research on virus–host interactions, particularly with approach of systems biology. Virus-host systems biology can make predictions on host responses and dynamic interactions between viruses and hosts by computational modelling. It is interesting to note that modelling are expected to be done at different levels of abstraction like genes, proteins, cells, and organisms [46]. *Ayurvedic* foundational framework of '*Dosha-Dhatu-Mala-Agni-Srotas*' can serve as a model for these proposed studies. *Ayurvedic* foundational concepts have great potential and hence such studies can indeed make paradigm shift. Conservation of *Agni-Bala* and homeostasis of *Prana-Rakta-Shukra-Ojus* quadrant can be best host centric approach to improve clinical outcomes in COVID-19.

Source(s) of funding

None.

Conflicts of interest

None.

Acknowledgement

Authors are thankful to Dr Supriya Bhalerao & Prof Asmita Wele for inputs on scientific writing.

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